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Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 45/46

INFANRIX HEXA

International non-proprietary name: diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)

Procedure No: EMA/H/C/0296/P45/089 and EMA/H/C/0296/ P46 099

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. INTRODUCTION

GSK Biologicals' diphteria-tetanus-acellular pertussis, hepatitis B, inactivated polio and Hib (DTPa-HBV-IPV/Hib) vaccine, Infanrix Hexa, was licensed, via the centralised procedure, in the European Union on 23rd October, 2000.

Infanrix hexa is indicated for primary and booster vaccination of infants against diphteria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by Haemophilus influenza type b.

All clinical studies regarding Infanrix hexa submitted up to 01/2010 (FUM089, FUM099) in the context of the Article 45 and 46 procedures of the pediatric regulation have been reviewed during the renewal procedure Infanrix hexa EMEA/H/C/000296/R/0097.

2. SCIENTIFIC DISCUSSION

2.1. Clinical Studies

A total of 16 studies evaluating the commercial formulation of Infanrix hexa are included in the current report:

- Seven studies with Infanrix hexa which have been submitted to the CHMP in the context of Article 45 of the paediatric regulation. Of these, 5 studies were primary vaccination studies (DTPa- HBV- IPV- 055, - 063, - 070, - 075, - 093) and 2 studies were booster studies (DTPa-HBV- IPV- 083, - 103).
- Eight studies with Infanrix hexa with submission to the CHMP in the context of Article 46 of the paediatric regulation. Of these, 3 studies were primary vaccination studies (DTPa- HBV- IPV-100, - 106, - 116), two studies were booster studies (DTPa- HBV- IPV- 117 and - 120) and 3 studies (DTPa- HBV- IPV- 110, - 111 and - 112) are antibody persistence studies. It should be noted that partial data of studies DTPa- HBV- IPV- 110 and - 111 have previously been submitted to the CHMP (on 21 August 2008) in the context of providing long term immunogenicity of the hepatitis B component after the booster dose of Infanrix hexa. Since only long term immunogenicity of the hepatitis B component were discussed in that submission, immunogenicity and safety data of these studies have been taken into account in the current dossier.
- One study (HibMenC- TT- 015) where a booster dose of Infanrix hexa was co-administered with NeisVac-C will be submitted to the CHMP under Article 46 of the paediatric regulation for GSK Biologicals' HibMenC vaccine Menitorix.

Among the 16 clinical studies with Infanrix hexa included in the dossier:

Eight clinical studies have been conducted to evaluate Infanrix hexa administered as primary vaccination course to infants aged of 6 to 17 weeks at the time of first injection. Several vaccination schedules were used in different studies. A total of 2093 subjects were vaccinated with approximately 4670 doses of Infanrix hexa in all primary vaccination studies.

Five booster vaccination studies have been conducted to evaluate Infanrix hexa administered as a booster vaccine at the age of 11 months (third dose) or in the second year of life (fourth dose)

following priming with Infanrix hexa. A total of 994 subjects were vaccinated with a booster dose of Infanrix hexa. In these 5 trials, blood samples were to be taken prior the administration of the Infanrix hexa booster dose to evaluate the antibody persistence induced by primary vaccination course.

Three studies (DTPa-HBV-IPV-110, -111 and -112) assessed the long-term antibody persistence in healthy children 4 to 9 years old, previously vaccinated with four doses of Infanrix hexa in primary and booster course.

2.2. Results

Reactogenicity and immunogenicity of Infanrix hexa after primary vaccination course

In the 8 clinical studies evaluating Infanrix hexa administered as primary vaccination course, 1375 infants were administered Infanrix hexa alone and an additional 718 infants were administered Infanrix hexa with routine paediatric vaccines (Prevenar or OPV vaccine). The schedules that have been studied include those used in Europe: 2-3-4 months (2 trials), 2-4-6 months (2 trials), 3-4-5 months (3 trials) and 3-5+11 months (1 trial).

In two trials, Infanrix hexa was only given as part of the full 3-dose primary vaccination course (1st and 3rd primary dose and booster dose at 16-18 months in study DTPa- HBV-IPV- 093; 3rd primary dose in DTPa- HBV- IPV- 100).

The safety and reactogenicity of Infanrix hexa were evaluated in all 8 trials; immunogenicity was evaluated in 4 trials. It should be noted that in one study (DTPa- HBV- IPV- 093) not all antigens of Infanrix hexa were assessed.

All data were obtained using procedures similar to those described in the original registration dossier for Infanrix hexa; results from all studies can therefore validly be compared.

The overall reactogenicity profile of Infanrix hexa was comparable with data currently reported in section 4.8 of the SPC. The incidences of local and general solicited symptoms and the incidences of unsolicited events considered to be causally linked to the administration of Infanrix hexa were similar to those listed in the current SPC.

During the 8 primary vaccination studies included in this Overview, only one subject (in study DTPa-HBV- IPV- 100) reported two SAEs (febrile convulsion and exanthema subitum) that were considered as possibly related to Infanrix hexa vaccination by the investigator. These SAEs were not reported in a PSUR, because the relationship was unknown during the reporting period, since the study was blinded.

Reactogenicity and immunogenicity of Infanrix hexa after booster vaccination

In the 5 clinical studies evaluating the safety and immunogenicity of Infanrix hexa administered as a booster, a total of 994 subjects received the Infanrix hexa booster dose and all subjects were previously primed with Infanrix hexa. In 644 subjects aged 16-24 months, the booster dose was the fourth Infanrix hexa dose and in 350 subjects aged approximately 12 months, the booster dose was the third Infanrix hexa dose. In one study, the Infanrix hexa booster dose was co-administered with NeisVac-C (350 subjects).

In all 5 studies, a blood sample was taken prior the administration of the booster dose to evaluate the antibody persistence induced by the primary vaccination course.

The frequency and severity of the adverse events reported after booster vaccination in the 5 booster studies presented in this dossier were similar to those listed in the current SPC.

None of the subjects receiving a booster dose of Infanrix hexa reported a SAE that was considered as possibly related to the vaccine by the investigator.

The immune response after booster vaccination in these 5 studies was not different from what was initially reported, for all vaccine antigens.

Antibody persistence of Infanrix hexa after booster vaccination

In studies DTPa-HBV-IPV-110, -111 and –112, the long-term antibody persistence was assessed in healthy children aged 4 to 9 years old who had previously received a 3-dose primary vaccination course during infancy followed by a booster in the second year of life, with Infanrix hexa. In these 3 trials, a total of 704 subjects were included to evaluate the antibody persistence at 2.5 to 7.5 years after Infanrix hexa booster vaccination. In two studies (DTPa-HBV-IPV-110 and –111) antibody persistence was assessed against each vaccine component of Infanrix hexa, whereas in DTPa-HBV-IPV-112 this was only assessed against the hepatitis B component.

In these 3 studies, all subjects received a challenge dose of hepatitis B vaccine at the persistence time point.

The results show that persisting antibodies were present in 4 to 9 year-old children vaccinated during infancy with 4 doses of Infanrix hexa and the data are in line with what was reported in previous studies, for all vaccine antigens.

3. Rapporteur's Overall Conclusion and recommendation

The submitted paediatric studies do not influence the benefit risk for Infanrix hexa. The data provided are in line with what was previously reported with Infanrix hexa. Therefore, no changes to the SmPC or PIL are necessary and no other regulatory action is required.

The Rapporteur is of the opinion that the Article 45 and Article 46 procedures for Infanrix hexa can be considered closed.